

## INFORMATION DISCLOSURE STATEMENT

Applicant : Weiner et al.  
App. No : 10/761,787  
Filed : January 21, 2004  
For : USE OF N-DESMETHYLCLOZAPINE  
TO TREAT HUMAN  
NEUROPSYCHIATRIC DISEASE  
Examiner : J. M. Kim  
Art Unit : 1617

## CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

August 7, 2007

(Date)

Ryan E. Melnick, Reg. No. 58,621

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing in the above-identified application is a PTO/SB/08 Equivalent listing 209 references to be considered by the Examiner. Also enclosed are 179 foreign patent references and/or non-patent literature as listed on the Information Disclosure Statement.

An English translation of DE 2316438 (reference no. 39) was not available. The English-language equivalent of this reference is believed to be found in U.S. Patent No. 3,962,248 (reference no. 2).

An English translation of WO 2004/078216 (reference no. 69) was not available. The reference contains an English language abstract. Furthermore, the relevant portions of the reference are believed to be the chemical structures found on page 6.

This Information Disclosure Statement is being filed before the receipt of a first Office Action on the merits, and presumably no fee is required. If a first Office Action on the merits

**Appl. No.** : 10/761,787  
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**Docket No.** ACADIA.031A  
**Customer No.** 20,995

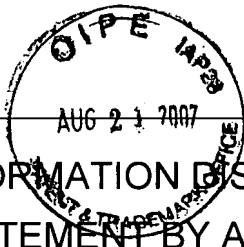
was mailed before the mailing date of this Statement, the Commissioner is authorized to charge the fee set forth in 37 C.F.R. § 1.17(p) to Deposit Account No. 11-1410.

Respectfully submitted,  
KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 8-7-07

By: Ryan E. Melnick  
Ryan E. Melnick  
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>	Application No.	10/761,787
	Filing Date	January 21, 2004
	First Named Inventor	Weiner et al.
	Art Unit	1617
(Multiple sheets used when necessary)	Examiner	J. M. Kim
SHEET 1 OF 11	Attorney Docket No.	ACADIA.031A

U.S. PATENT DOCUMENTS					
Examiner Initials	Cite No.	Document Number Number - Kind Code (if known) Example: 1,234,567 B1	Publication Date MM-DD-YYYY	Name of Patentee or Applicant	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
	1	3,444,169	05-13-1969	Howell et al.	
	2	3,962,248	06-08-1976	Schneider	
	3	4,045,445 A	08-30-1977	Hardy, Jr. et al.	
	4	4,096,261 A	06-20-1978	Horrom et al.	
	5	4,097,597 A	06-27-1978	Horrom et al.	
	6	4,263,207 A	04-21-1981	Rokach et al.	
	7	4,404,137 A	09-13-1983	Chakrabarti et al.	
	8	5,300,422 A	04-05-1994	Gerson et al.	
	9	5,393,752 A	02-28-1995	Liegeois et al.	
	10	5,700,445 A	12-23-1997	Fu et al.	
	11	5,707,798	01-13-1998	Brann	
	12	5,817,655 A	10-06-1998	Chakrabarti et al.	
	13	6,479,488	11-12-2002	Di-Fabio et al.	
	14	2002/0037886	03-28-2002	Andersson et al.	
	15	2004/0224942	11-11-2004	Weiner et al.	
	16	2005/0085463	04-21-2005	Weiner et al.	
	17	2005/0192268 A1	09-01-2005	Ek et al.	
	18	2005/0250767	11-10-2005	Weiner et al.	
	19	2005/0282800 A1	12-22-2005	Tolf et al.	
	20	2006/063755 A1	03-23-2006	Edgar Dale et al.	
	21	2006/063754 A1	03-23-2006	Edgar Dale et al.	
	22	2006/0069083	03-30-2006	Steiner et al.	
	23	2006/0111342	05-25-2006	Argentine et al.	
	24	2006/0194784 A1	08-31-2006	Ek et al.	
	25	2006/0199808 A1	09-07-2006	Tolf et al.	
	26	2006/0199798 A1	09-07-2006	Ek et al.	
	27	2006/0205714 A1	09-14-2006	Tolf et al.	
	28	2006/0233843	10-19-2006	Conn et al.	
	29	2006/0252744 A1	11-09-2006	Burstein	

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	30	2007/0105836 A1	05-10-2007	Pettersson, et al.	

## FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Country Code-Number-Kind Code Example: JP 1234567 A1	Publication Date MM-DD-YYYY	Name of Patentee or Applicant	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T <sup>1</sup>
	31	CH 240 228 A	12-15-1945	CIBA Aktiengesellschaft		
	32	CH 422 793 A	10-31-1966	Dr. A. Wander AG		
	33	CH 476 753 A	08-15-1969	Dr. A. Wander AG		
	34	CH 493 538 A	07-15-1970	American Cyanamid Company		
	35	CH 499 539 A	11-30-1970	Dr. A. Wander AG		
	36	CH 585 222 A5	02-28-1977	Dr. A. Wander AG		
	37	CH 601 288 A5	07-14-1978	Sandoz AG		
	38	DD 133 235 A1	12-20-1978	Rueger et al.		
	39	DE 2316438+A18	10-11-1973	Wander AG, Bern		
	40	DE 26 25 258 A1	12-09-1976	F. Hoffmann-La Roche & Co AG		
	41	EP 0 240 228 A	10-07-1987	ICI Americas Inc.		
	42	EP 1 725 952 A1	11-29-2006	Ishiyama		
	43	EP 1 726 952 A1	11-29-2006	Dainippon Sumitomo Pharma Co., Ltd. Osaka		
	44	FR 1 334 944 A	08-16-1963	Dr. A. Wander S.A.		
	45	FR 2 222 102 A	10-18-1974	Wander SA, CH		
	46	FR 51	04-06-1964	Wander		X
	47	FR 870 763 A	03-24-1942	Zeiss Ikon Aktiengesellschaft		
	48	FR 939 595 A	11-18-1948	Dr. A. Wander AG		
	49	GB 1 216 523 A	12-23-1970	Dr. A. Wander AG		
	50	GB 1 554 275 A	10-17-1979	Sandoz Ltd		
	51	GB 1 006 156	09-29-1965	Wander		
	52	GB 2 292 685	03-06-1996	Sankyo Company Limited		
	53	WO 93/07143 A1	04-15-1993	Therabel Research S.A./N.V.		

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	54	WO 95/17400 A1	06-29-1995	Allelix Biopharma		
	55	WO 96/29316 A1	09-26-1996	Wikstroem et al.		
	56	WO 99/50247 A1	10-07-1999	Acadia Pharmaceuticals Inc.		
	57	WO 01/29036 A2	04-26-2001	Medical Research Council Technology		
	58	WO 01/83472 A1	11-08-2001	Acadia Pharmaceuticals Inc.		
	59	WO 02/060870 A2	08-08-2002	Adolor Corporation		
	60	WO 03/000670 A1	01-03-2003	Neuromolecular Inc.		
	61	WO 03/070249 A1	08-28-2003	Nowak et al.		
	62	WO 03/082877 A1	10-09-2003	Eli Lilly and Company		
	63	WO 2004/026030 A2	04-01-2004	FMC Corporation		
	64	WO 2004/026030 A2	04-01-2004	FMC Corporation		
	65	WO 2004/056182 A1	07-08-2004	Basf Aktiengesellschaft		
	66	WO 2004/064738 A3	08-05-2004	Acadia Pharmaceuticals, Inc.		
	67	WO 2004/064753 A2	08-05-2004	Acadia Pharmaceuticals, Inc.		
	68	WO 2004/073639 A2	09-02-2004	Merck & Co. Inc.		
	69	WO 2004/078216 A2	09-16-2004	Rina Netzwerk RNA-Technologien GMBH		
	70	WO 2005/002586 A1	01-13-2005	Astrazenca AB		
	71	WO 2005/063254 A2	07-14-2005	Acadia Pharmaceuticals, Inc.		
	72	WO 2005/103041 A2	11-03-2005	Hypnion Inc.		
	73	WO 2006/034414 A2	03-30-2006	Hypnion Inc.		
	74	WO 2006/081327 A2	08-03-2006	University of Vermont and State Agricultural College		
	75	WO 2006/088786 A2	08-24-2006	Combinatorx, Incorporated		

### NON PATENT LITERATURE DOCUMENTS

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	76	Alves-Rodrigues A, Leurs R, Willems E and Timmerman H (1996). Binding of clozapine metabolites and analogues to the histamine H3 receptor in rat brain cortex. <i>Archiv der Pharmazie</i> , 329: 413-416	

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	77	Anonymous, Certificate of Analysis: N-Desmethylozapine (2003), Internet article, Database accession no. 2003: 2066817, Order Number D292000	
	78	Anonymous, Morphanthridine. Research Disclosure, 258:512-14 (1985)	
	79	Anonymous, Piperazinyldibenzazepine. Research Disclosure, 192:158-9 (1980)	
	80	Ashby, C.R. et al., Pharmacological actions of the atypical antipsychotic drug clozapine: A review, Synapse, 24:349-394 (1996)	
	81	Baldessarini RJ, Centorrino F, Flood JG, Volpicelli SA, Huston-Lyons D and Cohen BM (1993). Tissue concentrations of clozapine and its metabolite in the rat. <i>Neuropsychopharm</i> , 9: 117-124	
	82	Baldessarini, R., J., and Frankenburg, F., R. (1991) Clozapine. A novel antipsychotic agent. <i>New. Engl. J. Med.</i> , 324(11): 746-754	
	83	Baumeister AA, Francis JL. Historical development of the dopamine hypothesis of schizophrenia. <i>J Hist Neurosci</i> . 2002 Sep;11(3):265-77	
	84	Berkeley JL and Levey AI (2003). Cell-Specific Extracellular Signal-regulated Kinase Activation by Multiple G Protein-coupled receptor Families in Hippocampus. <i>Mol Pharm</i> , 63: 128-135	
	85	Berkeley JL, Gomez J, Wess J, Hamilton SE, Nathanson NM and Levey AI (2001). M1 Muscarinic Acetylcholine Receptors Activate Extracellular Signal-Regulated Kinase in CA1 Pyramidal Neurons in Mouse Hippocampal Slices. <i>Mol Cell Neurosci</i> , 18: 512-524	
	86	Birdsall, N.J.M. et al., Subtype-selective positive cooperative interactions between brucine analogs and acetylcholine at muscarinic receptors: Functional studies, <i>Molecular Pharmacology</i> , 55(4):778-786 (1999)	
	87	Bodick NC, Offen WW, Levey AI, Cutler NR, Gauthier SG, Satlin A, Shannon HE, Tollefson GD, Rasmussen K, Bymaster FP, Hurley DJ, Potter WZ, Paul SM (1997) Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. <i>Arch Neurol</i> 54:465-473	
	88	Bolden C, Cusack B, Richelson E (1991) Clozapine is a potent and selective muscarinic antagonist at the five cloned human muscarinic acetylcholine receptors expressed in CHO-K1 cells. <i>Eur J Pharmacol</i> 192:205-206	
	89	Bondesson U, Lindstrom LH (1988) Determination of clozapine and its N-demethylated metabolite in plasma by use of gas chromatography-mass spectrometry with single ion detection. <i>Psychopharmacology</i> 95:472-475	
	90	Bonner TI, Buckley NJ, Young AC, Brann MR (1987) Identification of a family of muscarinic acetylcholine receptor genes. <i>Science</i> 237:527-532	
	91	Bonner, T.I. et al., Cloning and expression of the human and rat m5 muscarinic acetylcholine receptor genes, <i>Neuron</i> , 1:403-410 (1988)	
	92	Bourin Michel et al., Cyamemazine as an anxiolytic drug on the elevated plus maze and light/dark paradigm in mice (2001), <i>Behavioural Brain Research</i> , 124(1):87-95	
	93	Brauner-Osborne H, Ebert B, Brann MR, Falch E, Krogsgaard-Larsen P (1996) Functional partial agonism at cloned human muscarinic acetylcholine receptors. <i>Eur J Pharmacol</i> 313:145-150	

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	94	Brown, J., H., and Taylor, P., (1996) Muscarinic receptor agonists and antagonists, in The pharmacological basis of therapeutics. Hardiman, J., G., and Limbird, L., E., editors, Mcgraw-Hill, New York, pp. 141-161	
	95	Buerki, H.R. et al., Effects of clozapine and other dibenzo-epines on central dopaminergic and cholinergic systems. Structure-activity relationships. <i>Arzneimittel-Forschung</i> , 27(8):1561-5 (1977)	
	96	Bun H, Disdier B, Aubert C and Catalin J (1999). Interspecies variability and drug interactions of clozapine metabolism by microsomes. <i>Fundam Clin Pharmacol</i> . 13: 577-581	
	97	Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. <i>J Pharmacol Exp Ther</i> . 2002 Jul;302(1):381-9	
	98	Burstein et al., J. Pharmacol. Exp. Ther. 315(3):1278-1287 (2005)	
	99	Bymaster FB, Carter PA, Yamada M, Gomeza J, Wess J, Hamilton S, Nathanson NM, McKinzie DL, Felder CC (2003) Role of specific muscarinic receptor subtypes in cholinergic parasympathomimetic responses, in vivo phosphoinositide hydrolysis, and pilocarpine-induced seizure activity. <i>Eur J Neurosci</i> 17:1403-1410	
	100	Bymaster FP, Felder C, Ahmed S and McKinzie D (2002). Muscarinic Receptors as a Target for Drugs Treating Schizophrenia. <i>Curr Drug Targ CNS Neurol Dis</i> , 1: 163-181	
	101	Bymaster, F.P., Potential role of muscarinic receptors in schizophrenia, <i>Life Sciences</i> , 64(6/7):527-534 (1999)	
	102	Capuano, <i>Molecules</i> 4:329-332 (1999)	
	103	Carlsson A (1978) Antipsychotic drugs, neurotransmitters, and schizophrenia. <i>Am J Psychiatry</i> 135(2):164-173	
	104	Casey DE. Tardive dyskinesia: pathophysiology and animal models. <i>J Clin Psychiatry</i> 2000;61 Suppl 4:5-9	
	105	Centorrino, F., Baldessarini, R., J., Kando, J., C., et. al. (1994) Clozapine and metabolites: concentrations in serum and clinical findings during treatment of chronically psychotic patients. <i>J. Clin. Psychopharmacol.</i> 14: 119-125	
	106	Charfi F, Cohen D, Houeto JL, Soubrie C, Mazet P. Tardive dystonia induced by atypical neuroleptics: a case report with olanzapine. <i>J Child Adolesc Psychopharmacol</i> . 2004 Spring;14(1):149-52	
	107	Christopoulos, A., Allosteric binding sites on cell-surface receptors: Novel targets for drug discovery, <i>Nature Reviews. Drug Discovery</i> , 1:198-210 (2002)	
	108	Creese I, Burt DR and Snyder SH (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. <i>Science</i> 192: 481-483	
	109	Daeffler L, Landry Y. Inverse agonism at heptahelical receptors: concept, experimental approach and therapeutic potential. <i>Fundam Clin Pharmacol</i> . 2000 Mar-Apr;14(2):73-87	
	110	Davis RE, Emmerling MR, Jaen JC, Moos WH, Spiegel K (1993) Therapeutic intervention in dementia. <i>Crit Rev Neurobiol</i> 7:41-83	
	111	Davis, R E; Doyle, P D; Carroll, R T; Emmerling, M R; Jaen, J. Cholinergic therapies for Alzheimer's disease: Palliative or disease altering? <i>Arzneimittel-Forschung</i> , 45, 425-431, 1995	

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	112	Durif F. et al., Low-dose clozapine improves dyskinesias in Parkinson's disease, <i>Neurology</i> vol. 48, no. 3, 1997, pages 658-662	
	113	Eglen, R., M., Choppin, A., and Watson, N., (2001) Therapeutic opportunities from muscarinic receptor research. <i>Trends Pharmacol. Sci.</i> <b>22(8)</b> : 409-414	
	114	Fabrazzo M, La Pia S, Monteleone P, Esposito G, Pinto A, De Simone L, Bencivenga R, Maj M (2002) Is time course of clozapine response correlated to the time course of plasma clozapine levels? A one-year prospective study in drug-resistant patients with schizophrenia. <i>Neuropsychopharmacology</i> 27:1050-1055	
	115	Felder CC, Bymaster FP, Ward J and DeLapp N (2000). Therapeutic Opportunities for Muscarinic Receptors in the Central Nervous System. <i>J Med Chem</i> , 43: 4333-4353	
	116	Felder, C.C. et al., Elucidating the role of muscarinic receptors in psychosis, <i>Life Sciences</i> , 68:2605-2613 (2001)	
	117	Frazier JA, Glassner Cohen L, Jacobsen L, Grothe D, Flood J, Baldessarini RJ, Piscitelli S, Kim GS, Rapoport JL (2003) Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. <i>J Clin Psychopharmacol</i> 23(1):87-91	
	118	Fritze J, Elliger T (1995) Pirenzepine for clozapine-induced hypersalivation. <i>Lancet</i> 346:1034	
	119	Gauch R, Michaelis W (1971) The metabolism of 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine (clozapine) in mice, dogs, and human subjects. <i>II Farmaco</i> 26:667-681	
	120	Gerber DJ, Sotnikova TD, Gainetdinov RR, Huang SY, Caron MG, Tonegawa S (2001) Hyperactivity, elevated dopaminergic transmission, and response to amphetamine in M1 muscarinic acetylcholine receptor-deficient mice. <i>Proc Natl Acad Sci USA</i> 98(26):15312-15371	
	121	Gerlach J. et al, Intolerance to Neuroleptic Drugs: The art of avoiding extrapyramidal syndromes, <i>European Psychiatry</i> , vol. 10, no. Supp 1, (1994) pages 27S-31S	
	122	Gourzis Philippos et al., Quetiapine in the treatment of focal tardive dystonia induced by other atypical antipsychotics - A report of 2 cases, <i>Clinical Neuropharmacology</i> , vol. 28, no. 4, July 2005, pages 195-196	
	123	Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? <i>Am J Psychiatry</i> 153:321-330	
	124	Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY (1993) Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. <i>Biol Psychiatry</i> 34:702-712	
	125	Hall DA, Strange PG Evidence that antipsychotic drugs are inverse agonists at D2 dopamine receptors. <i>Br J Pharmacol.</i> 1997 Jun;121(4):731-6	
	126	Hamilton SE and Nathanson NM (2001). The M1 Receptor is required for Muscarinic Activation of Mitogen-activated Protein (MAP) Kinase in Murine Cerebral Cortical Neurons. <i>J Biol Chem</i> , 276: 15850-15853	
	127	Harrison TS & Perry CM Aripirazole: A review of its use in schizophrenia and schizoaffective disorder. <i>Drugs</i> 2004 64(15):1715-1736	
	128	Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY (1993) Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. <i>J Clin Psychopharmacol</i> 13:383-390	

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	129	Heinrichs DW, Hanlon TE, Carpenter WT (1984) The Quality of Life Scale: an instrument for rating the schizophrenia deficit syndrome. <i>Schizophr Bull</i> 10:388-398	
	130	Hunziker F, Fisher, E., and Schmutz, J. (1967) 11-amino-5H-dibenzo[b,e]-1,4-diazepine. Mitteilung uber siebengliedrige Heterocyklen. <i>Helv. Chim. Acta</i> , 50:1588-1599	X
	131	Inoue T, Domae M, Yamada K, Furukawa T. Effects of the novel antipsychotic agent 7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597) on prolactin release from the rat anterior pituitary gland. <i>J Pharmacol Exp Ther</i> . 1996 Apr;277(1):137-43	
	132	Jacobson, M.A. et al., Mapping the interaction site of M1 muscarinic receptor allosteric agonists, abstract, Society for Neuroscience Annual Meeting, San Diego, CA, Oct 23-27, 2004	
	133	Jakubik, J. et al., Allosteric modulation by persistent binding of xanomeline of the interaction of competitive ligands with the M1 muscarinic acetylcholine receptor," <i>Journal of Pharmacology and Experimental Therapeutics</i> , 301(3):1033-1041 (2002)	
	134	Jann, M., W., Grimsley, S., R., Gray, E., C., and Chang, W. (1993) Pharmacokinetic and pharmacodynamics of clozapine. <i>Clin. Pharmacokinet</i> . 24(2): 161-176	
	135	Jensen, A., A., Spalding, T., A., Burstein E., S., et. al. (2000) Functional importance of the Ala(116)-Pro(136) region in the calcium-sensing receptor. Constitutive activity and inverse agonism in a family C G-protein-coupled receptor. <i>J Biol Chem</i> . 275(38): 29547-55	
	136	Kane J, Honigfeld G, Singer J, Meltzer H, Clozaril Collaborative Study Group (1988) Clozapine for the treatment-resistant schizophrenic. <i>Arch Gen Psychiatry</i> 45:789-796	
	137	Kuoppamaki M, Syvalahti E, Hietala J (1993) Clozapine and N-desmethyloclozapine are potent 5-HT <sub>1C</sub> receptor antagonists. <i>Eur J Pharmacol</i> 245:179-182	
	138	Lammers et al., Coadministration of clozapine and fluvoxamine in psychotic patients - clinical experience (1999), <i>Pharmacopsychiatry</i> , 32(2):76-77	
	139	Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, Gonzalez AM, Sibley DR, Mailman RB. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. <i>Neuropsychopharmacology</i> . 1999 Jun;20(6):612-27	
	140	Lazareno, S. et al., Towards a high-affinity allosteric enhancer at muscarinic M1 receptors, <i>J. of Molecular Neuroscience</i> , 19:123-127 (2002)	
	141	Lee MA, Jayathilake K, Meltzer HY (1999) A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. <i>Schizophr Res</i> 37:1-11	
	142	Leucht S, Wahlbeck K, Hamann J, Kissling W (2003) New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. <i>Lancet</i> 361(9369):1581-1589	
	143	Liao et al. <i>J. Med. Chem.</i> 1997, 40, 4146-4153	
	144	Liao et al. <i>J. Med. Chem.</i> 1999, 42, 2235-2244	
	145	Lin, G., Characterization of metabolites of clozapine N-oxide in the rat by micro-column high performance liquid chromatography/mass spectrometry with electrospray interface (1996), <i>J. Pharmaceutical and Biomedical Analysis</i> , 14:1561-1577	
	146	Lu, ML, Dosing Strategies of Clozapine-fluvoxamine cotreatment (2002), <i>Journal of Clinical Psychopharmacology</i> , Williams and Wilkins, 22(6):626-628	

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	147	Ma JN, Currier EA, Essex A, Feddock M, Spalding TA, Nash NR, Brann MR, Burstein ES. Discovery of novel peptide/receptor interactions: identification of PHM-27 as a potent agonist of the human calcitonin receptor. <i>Biochem Pharmacol.</i> 2004 Apr 1;67(7):1279-84	
	148	Mauri MC, Volonteri LS, Dell'Osso B, Regispani F, Papa P, Baldi M, Bareggi SR (2003) Predictors of clinical outcome in schizophrenic patients responding to clozapine. <i>J Clin Psychopharmacol</i> 23(6):660-664	
	149	Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Zahur Islam M, Kane J, Krishnan R, Lindenmayer JP, Potkin S (2003) Clozapine treatment for suicidality in schizophrenia. <i>Arch Gen Psychiatry</i> 60:82-91	
	150	Meltzer HY, Matsubara S, Lee JC (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. <i>J Pharmacol Exp Ther</i> 251:238-246	
	151	Meltzer HY. What's atypical about atypical antipsychotic drugs? <i>Curr Opin Pharmacol.</i> 2004 4(1):53-7	
	152	Merck Manual, The, seventeenth Edition (1999), Merck Research Laboratories, pp. 1563-1573	
	153	Miller RJ, Hiley CR (1974) Anti-muscarinic properties of neuroleptics and drug-induced Parkinsonism. <i>Nature</i> 248:596-597	
	154	Milligan G, MacEwan DJ, Mercouris M, Mullaney I. Inverse agonism at adrenergic and opioid receptors: studies with wild type and constitutively active mutant receptors. <i>Receptors Channels.</i> 1997;5(3-4):209-13	
	155	Mirza NR, Peters D, Sparks RG (2003) Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. <i>CNS Drug Rev</i> 9(2):159-186	
	156	Mosier KE, Song J, McKay G, Hubbard JW and Fang J (2003). Determination of clozapine, and its metabolites, N-desmethylozapine and clozapine N-oxide in dog plasma using high-performance liquid chromatography. <i>J Chromat B</i> , 783: 377-382	
	157	Nordin C, Alme B, Bondesson U (1995) CSF and serum concentrations of clozapine and its demethyl metabolite: a pilot study. <i>Psychopharmacology</i> 122:104-107	
	158	Olianas MC, Maullu C, Onali P (1999) Mixed agonist-antagonist properties of clozapine at different human cloned muscarinic receptor subtypes expressed in chinese hamster ovary cells. <i>Neuropsychopharmacology</i> 20(3):263-270	
	159	Olianas, M.C. et al., Effects of clozapine on rat striatal muscarinic receptors coupled to inhibition of adenyl cyclase activity and on the human cloned m4 receptor, <i>Brit. J. Pharmacol.</i> , 122:401-408 (1997)	
	160	Özdemir, V., et al., "CYP1A2 Activity as Measured by a Caffeine Test Predicts Clozapine and Active Metabolite Norclozapine Steady-State Concentration in Patients With Schizophrenia," <i>Journal of Clinical Psychopharmacology</i> , 21:4(398-407), August 2001	
	161	Parkinson Study Group, The (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's Disease. <i>N Engl J Med</i> 340:757-763	
	162	Perry PJ, Miller DD, Arndt SV, Cadoret RJ (1991) Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. <i>Am J Psychiatry</i> 148(2):231-135	
	163	Pfeiffer CC, Jenney EH (1957) The inhibition of the conditioned response and the counteraction of schizophrenia by muscarinic stimulation of the brain. <i>Ann NY Acad Sci</i> 66:753-764	

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	164	Schaber, G. et al., Isolation and identification of clozapine metabolites in patient urine, Drug Metabolism and Disposition, 29(6):923-931 (2001)	
	165	Schlicker E and Marr I (1996). The moderate affinity of clozapine at H3 receptors is not shared by its two major metabolites and by structurally related and unrelated atypical neuroleptics. <i>Naunyn-Sch Arch Pharmacol</i> , 353: 290-294	
	166	Schmutz, J, Neuroleptic Piperazinyl-dibenzo-azepines, Arzneimittel Forschung. Drug Research, 25(5):712-720 (1975)	
	167	Seeman P, Lee T, Chau-Wong M and Wong K (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. <i>Nature</i> 261: 717-719	
	168	Serretti A, De Ronchi D, Lorenzi C, Berardi D. New antipsychotics and schizophrenia: a review on efficacy and side effects. <i>Curr Med Chem</i> . 2004 Feb;11(3):343-58	
	169	Shannon HE, Bymaster FP, Calligaro DO, Greenwood B, Mitch CH, Sawyer BD, Ward JS, Wong DT, Olesen PH, Sheardown MJ, Swedberg MDB, Suzdak PD, Sauerberg P (1994) Xanomeline: a novel muscarinic receptor agonist with functional selectivity for M1 receptors. <i>J Pharmacol Exp Ther</i> 269(1):271-281	
	170	Shannon HE, Rasmussen K, Bymaster FP, Hart JC, Peters SC, Swedberg MD, Jeppesen L, Sheardown MJ, Sauerberg P, Fink-Jensen A (2000) Xanomeline, an M(1)/M(4) preferring muscarinic cholinergic receptor agonist, produces antipsychotic-like activity in rats and mice. <i>Schizophr Res</i> 42:249-259	
	171	Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. <i>Neuropsychopharmacology</i> . 2003 Aug;28(8):1400-11	
	172	Shapleske J, Mickay AP, McKenna PJ. Successful treatment of tardive dystonia with clozapine and clonazepam. <i>Br J Psychiatry</i> . 1996 Apr;168(4):516-8	
	173	Smits et al., Characterization of the histamine H <sub>4</sub> receptor binding site. Part 1. Synthesis and pharmacological evaluation of dibenzodiazepine derivatives (2006), J. Med. Chem. 49:4512-4516	
	174	Snyder S, Greenberg D, Yamamura HI (1974) Anti-schizophrenic drugs and brain cholinergic receptors. Affinity for muscarinic sites predicts extrapyramidal effects. <i>Arch Gen Psychiatry</i> 31:58-61	
	175	Spalding et al., Mol. Pharm. 70:1974-83 (2006)	
	176	Spalding TA, Trotter C, Skjaerbaek N, Messier TL, Currier EA, Burstein ES, Li D, Hacksell U, Brann MR (2002) Discovery of an ectopic activation site on the M(1) muscarinic receptor. <i>Mol Pharmacol</i> 61:1297-1302	
	177	Spina E, Avenoso A, Facciola G, Salemi M, Scordo MG, Ancione M, Madia AG, Perucca E (2001) Relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and clinical response in patients with schizophrenia. <i>Psychopharmacology</i> 153:238-243	
	178	Spina, E., et al., "Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia," International Clinical Psychopharmacology, 13:141-145, 1998	
	179	Sridhar, N, New promises for schizophrenia therapy, Drug Discovery Today, 7(4):215-216 (2002)	
	180	Stanhope, K.J., The muscarinic receptor agonist xanomeline has an antipsychotic-like profile in the rat, JPET, 299(2):782-792 (2001)	

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	181	Steiner, Gerd et al., Tricyclic epines. Novel (E)- and (Z)-11H-dibenz[b,e]azepines as potential central nervous system agents. Variation of the basic side chain. <i>Journal of Medicinal Chemistry</i> , 29(10):1877-88 (1986)	
	182	Strange PG. Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. <i>Pharmacol Rev.</i> 2001 Mar;53(1):119-33	
	183	Sur C, Mallorga PJ, Wittmann M, Jacobsen MA, Pascarella D, Williams JB, Brandish PE, Pettibone DJ, Scolnick EM and Conn PJ (2003). N-desmethylozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. <i>PNAS</i> , 100: 13674-13679	
	184	Tamminga CA, Carlsson A. Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. <i>Curr Drug Targets CNS Neurol Disord.</i> 2002 Apr;1(2):141-7	
	185	Tamminga CA. Partial dopamine agonists in the treatment of psychosis. <i>J Neural Transm.</i> 2002 Mar;109(3):411-20	
	186	Trugman JM, Leadbetter R, Zalis ME, Burgdorf RO, Wooten GF. Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. <i>Mov Disord.</i> 1994 Jul;9(4):441-6	
	187	Warawa E J. et al: Behavioral approach to nondyskinetic dopamine antagonists: Identification of Seroquel, <i>Journal of Medicinal Chemistry</i> , American Chemical Society, vol. 44, Feb 2001 pages 372-389	
	188	Weigmann H, Härter S, Fischer V, Dahmen N and Hiemke C (1999). Distribution of clozapine and desmethylozapine between blood and brain in rats. <i>Eur Neuropsychopharm</i> , 9: 253-256	
	189	Weigmann, H., et al., "Does the pharmacologically active N-demethylated metabolite of clozapine pass the blood-brain barrier?" <i>Pharmacopsychiatry</i> , and "20th Symposium of AGNP, Nuremberg, Germany," 30:5(233), September 1997	
	190	Weiner D M. et al., The role of M1 muscarinic receptor agonism of N-desmethylozapine in the unique clinical effects of clozapine, <i>Psychopharmacology</i> , vol. 177, no. 1-2, December 2004, pages 207-216, published online July 16, 2004.	
	191	Weiner DM, Burstein ES, Nash N, Croston GE, Currier EA, Vanover KE, Harvey SC, Donohue E, Hansen HC, Andersson CM, Spalding TA, Gibson DFC, Krebs-Thomson K, Powell, SB, Geyer MA, Hacksell U, Brann MR (2001) 5-hydroxytryptamine <sub>2A</sub> receptor inverse agonists as antipsychotics. <i>J Pharmacol Exp Ther</i> 299:268-276	
	192	Weiner DM, Levey AI, Brann MR (1990) Expression of muscarinic receptor acetylcholine and dopamine receptor mRNA's in rat basal ganglia. <i>Proc Natl Acad Sci USA.</i> 87:7050-7054	
	193	Weissman JT, Ma J, Essex A, Gao Y, Burstein ES (2003) G-protein-coupled receptor-mediated activation of rap GTPases: characterization of a novel Gi regulated pathway. <i>Oncogene</i> 23(1):241-249	
	194	Wellendorph P, Goodman MW, Burstein ES, Nash NR, Brann MR, Weiner DM (2002) Molecular cloning and pharmacology of functionally distinct isoforms of the human histamine H3 receptor. <i>Neuropharmacology</i> 42:929-940	
	195	Wong AH, Van Tol HH (2003) Schizophrenia: from phenomenology to neurobiology. <i>Neurosci Biobehav Rev</i> 27(3):269-306	
	196	Wong G, Kuoppamäki M, Hietala J, Luddens H, Syvälahti E and Korpi ER (1996). Effects of clozapine metabolites and chronic clozapine treatment on rat brain GABAA receptors. <i>Eur J Pharm</i> , 314: 319-323	
	197	Young CD, Meltzer HY and Deutch AY (1997). Effects of desmethylozapine on Fos protein expression in the forebrain: In vivo biological activity of the clozapine metabolite. <i>Neuropsychopharm</i> , 19: 99-103	

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	198	Zeng, X.P., et al., Muscarinic m4 receptor activation by some atypical antipsychotic drugs, E. Journal of Pharmacol., 321:349-354 (1997)	
	199	Zorn SH, Jones SB, Ward KM, Liston DR (1994) Clozapine is a potent and selective muscarinic M4 receptor agonist. <i>Eur J Pharmacol</i> 269:R1-R2	
	200	International Search Report, PCT/US2006/012463, dated 09-13-2006.	
	201	International Search Report, PCT/US2004/001509 dated 10-08-2004.	
	202	International Search Report, PCT/US2005/027645 dated 01-20-2006.	
	203	International Search Report, PCT/US2005/010876, dated 12-16-2005.	
	204	International Search Report, PCT/US2004/043224, dated 08-12-2005.	
	205	International Search Report, PCT/US2006/042464, dated 03-08-2007.	
	206	European Search Report, 04704073.8, dated 12-20-2006.	
	207	European Search Report, 04704073.8, dated 05-31-2006	
	208	Copy of Application No. 11/671,405.	
	209	Copy of Application No. 11/733,476.	

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